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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/922,067	MACPHEE ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,26 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *29 and 30* is/are allowed.

6)☒ Claim(s) *25,26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 25-26, 28-30 are currently pending in this application.

Applicants' amendments and arguments filed on 12-27-04, have been fully entered and considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the previous objections for lack of sequence compliance and rejections under 35 U.S.C. 112, 2nd paragraph as in view of claim amendments.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Specification

The disclosure is objected to because of the following informalities: Examiner notes that applicants have not updated the relationship of the instant application to its parent applications that have matured in to US patents. Examiner urges applicants to amend said information by providing the US patent number in response to this Office action. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-26, 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a lipoprotein associated phospholipase A2 (LPA-PLA2) having a molecular weight of from about 45-50 kDa and comprising amino acid sequence encoded by SEQ ID NO:9, does not reasonably provide enablement for any or all such LPA-PLA2 wherein said enzyme is encoded by a polynucleotide having at least 90% sequence identity with SEQ ID NO:9 or a polynucleotide having at least 90% sequence identity with nucleotides 929-1018 of SEQ ID NO:9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claim 25-26, 28 are so broad as to encompass any or all such LPA-PLA2 wherein said enzyme is encoded by a polynucleotide having at least 90% sequence identity with SEQ ID NO:9 or a polynucleotide having at least 90% sequence identity with nucleotides 929-1018 of SEQ ID NO:9. The scope of the claims is not commensurate with the enablement provided by

the disclosure with regard to the extremely large number of LPA-PLA2s broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single LPA-PLA2. It would require undue experimentation of the skilled artisan to first make polynucleotides that are 90% identical to SEQ ID NO:9 and use said polynucleotide to make said encoded polypeptides and use said polypeptides to determine the claimed polypeptides. The specification is limited to teaching the making of and use of the amino acid sequence encoded by SEQ ID NO:9 as a LPA-PLA2 but provides no guidance with regard to the making of polynucleotides that are 90% identical to SEQ ID NO:9 and use said polynucleotides to identify their encoded polypeptides occurring naturally. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function of a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of LPA-PLA2 encoded by SEQ ID NO:9 because the specification does not establish: (A) a rational and predictable scheme for isolating or purifying any LPA-PLA2 with an expectation of obtaining the desired biological function (B) regions of the protein structure encoded by SEQ ID NO:9 which may be modified without effecting its activity; (C) the general tolerance of LPA-PLA2s to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue on the amino acid sequence encoded by SEQ ID NO:9 with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polypeptide encoded by variants SEQ ID NO:9. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of LPA-PLA2 having

the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicant has traversed the above rejection. Applicant argues that amended claims 25 and 28 now recite "over the entire length of the enzyme" and also "human" and therefore Examiner's allegation that claim is broad is moot. While that may be so, claims are still directed to polypeptides that require the use variants of SEQ ID NO:9 for which there is no guidance as to how to make, in the specification. Next applicant argues, with respect to full length enzymes, the specification specifically discloses at page 16, lines 8-28, that a deduced peptide sequence obtained from a fetal spleen EST supports different full length sequences than a human embryo EST and a full-length lymphoma sequence. However, such arguments are moot in view of the revised rejection above. Applicants further submit that the skilled artisan would understand that enzymes with similar activities and derived from the same source can have varied amino acid sequences and provide examples of polymorphisms in nature. Applicants further submit that because variants and polymorphisms are understood to exist within a specific enzyme it is reasonable to assume that polypeptides recited in claims 25 and 28 may not have identical sequences to each other, even if they are obtained from the same species. While Examiner agrees with respect to all the above generalized information, he respectfully disagrees that such arguments would be persuasive to overcome the rejection. This is because applicants are not claiming out rightly, naturally occurring variants that are 90% or 95% identical to polypeptides encoded by full length SEQ ID NO:9. Instead they are claiming naturally occurring variants that are encoded by polynucleotides that are 90%

identical to SEQ ID NO:9. Contrary to applicant's arguments, those skilled in the art will first need to make polynucleotides 90% identical to SEQ ID NO:9 and this is what applicant has not taught or provided guidance to make, in the specification. Therefore, applicant's arguments are not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicant (i.e., polynucleotides that are 90% identical to SEQ ID NO:9) requires that one of ordinary skill in the art know or be provided with guidance regarding making changes to specific nucleotides over the entire length of SEQ ID NO:9 in order to arrive at polynucleotides that are 90% identical to SEQ ID NO:9, followed by the selection of which of the resulting infinite number of variants have the claimed property (i.e., encoding a polypeptide having phospholipase A2 activity). Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. Hence the above rejection is maintained.

Conclusion

Claims 29-30 are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-

0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

March 21, 2005